

A Study of β -Aminopropiophenone and Its Condensations with Nitromalonic Aldehyde

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
THE UNIVERSITY OF MICHIGAN

BY
EDGAR CLAY BRITTON

1918

EASTON, PA.,
ESCHENBACH PRINTING CO.
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The author wishes to express his indebtedness to Professor William J. Hale for the kindly interest which he has shown during the course of this research.

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I.

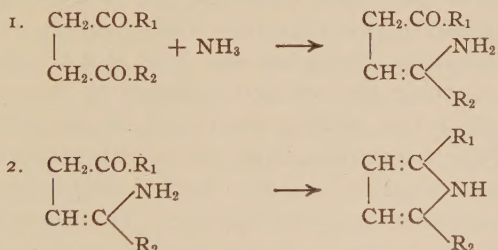
Historical Part.

The synthesis of pyrrole and its derivatives has received a great deal of attention during recent years, inasmuch as the pyrrole group or a hydrogenated form of this group, has been shown to be present in many naturally occurring substances, of which the proteins constitute by far the most important class.

An examination of the various methods by which pyrrole derivatives have been prepared, shows that only seven different types of synthesis have been generally used. It is our purpose to discuss only those synthetic methods which have shown general application in producing the pyrrole ring.

The best known synthetic method that has appeared in the literature during the last forty years, is found in the reaction devised by Knorr and Paal,¹ which takes place between γ -diketones and ammonia or substituted ammonias. This synthesis has found a large number of applications and only a few important examples will be given. From the historical as well as the theoretical standpoint, the synthesis by Knorr² of α, α' -dimethylpyrrole and the further investigation of the same compound by Knorr and Rabe³ is of special note. Knorr synthesized this pyrrole from diacetosuccinic ethyl ester and ammonia; it was shown later by Knorr and Rabe that an unsaturated amino ketone is first formed and this, by inner condensation, proceeds to the formation of α, α' -dimethyl- β, β' -dicarboethoxyl pyrrole. The latter compound being unstable in alkaline medium undergoes hydrolysis, loses the two carboethoxyl groups and produces α, α' -dimethylpyrrole.

The following reactions are representative of this type of synthesis:



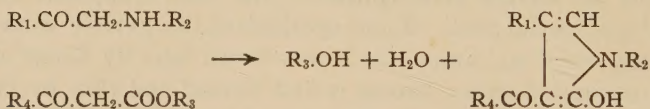
In place of ammonia in Reaction 1, substituted ammonias may be used, and accordingly, N-derivatives of pyrrole are produced. By the reaction of hydroxylamine and phenylhydrazine on diacetosuccinic ethyl ester,

¹ *Ber.*, 17, 2864 (1884); 18, 368, 2254 (1885).

² *Ibid.*, 18, 300 (1885).

³ *Ibid.*, 33, 3801 (1900).

Knorr¹ has synthesized α, α' -dimethyl-N-hydroxypyrrole and α, α' -dimethyl-N-phenylaminopyrrole. From the general reaction given above, we observe that an unsaturated amino ketone is first produced. However, there have been but two investigations in which this form of intermediate product has been isolated. Knorr and Rabe, as already stated have isolated one unsaturated amino ketone, and Borsche and Fels² have been fortunate enough to isolate several more of these ketones. These last two investigators, for example, have isolated the unsaturated amino ketones, resulting from the action of ammonia on ethylphenacyl-acetoacetoacetate, and also that one obtained from ethylacetonyl-benzoyl-acetate. They have shown further that these amino ketones suffer inner condensation, under suitable conditions, giving rise to pyrrole derivatives, and thus have confirmed the conclusion of Knorr as to the progress of the reaction. It is of interest, in this connection, to note that Almström³ has been able to modify the Knorr synthesis so as to include the use of secondary amines. The reaction follows a decidedly different direction, but may be considered as following the second step in the Knorr synthesis. Almström condensed compounds of the type $R_3\text{OOC}.\text{CH}_2.\text{CO}.\text{R}_4$ with compounds of the type $\text{R}_1.\text{CO}.\text{CH}_2.\text{NH}.\text{R}_2$ and found that the reaction proceeds as follows:



For example, he synthesized 5-hydroxy-4-acetyl-1,3-diphenylpyrrole from phenacyl aniline and acetoacetic ester. He also extended the reaction to several other systems.

Another method of obtaining pyrrole derivatives, scarcely less important than the one previously discussed, has been devised by Knorr.⁴ This synthesis consists in the reduction with hydrogen of a mixture of one mole of an isonitroso ketone and one mole of a ketone. Knorr and Lange⁵ have shown that the reaction proceeds in two steps, the first step being a reduction to a tertiary amine and the second being an inner condensation. Their conclusions rested on the experiments performed on the systems acetone-isonitrosoacetone, methyl ethyl ketone-isonitrosoacetone and acetone-isonitrosoacetophenone. The reaction between the compounds in any one of these systems upon reduction failed to produce products which gave the well known pine-shaving test for pyrrole. The

¹ *Ann.*, 236, 296 (1886); *Ber.*, 18, 1568 (1885).

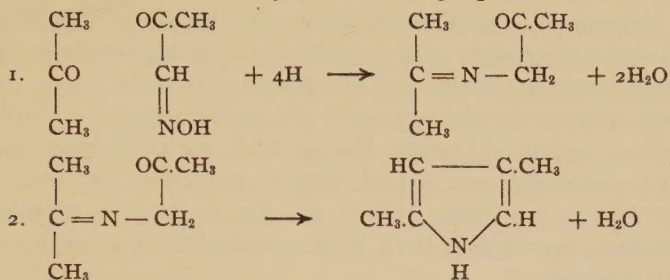
² *Ber.*, 39, 3877 (1906).

³ *Ann.*, 411, 350 (1916).

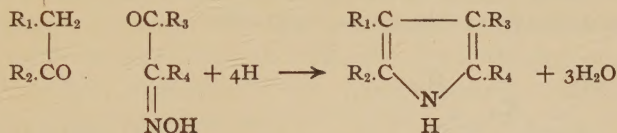
⁴ *Ibid.*, 236, 290 (1886); *Ber.*, 17, 1635 (1884).

⁵ *Ber.*, 35, 2998 (1902).

products, however, upon addition of concentrated sulfuric acid, gave compounds which were pyrroles. They concluded, therefore, that in the first step no pyrroles are produced, but in the second step sulfuric acid causes inner condensation presumably between hydrogen and oxygen, thus forming pyrrole derivatives. They represented the reaction between isonitrosoacetone and acetone by the following equations:



The general reactions for all syntheses by this method can be represented as follows:



The course of the general reaction as just outlined has been confirmed by the further researches of Knorr and also by the researches of Zanetti,¹ Veechi² and others. Several workers other than those already mentioned have extended this synthetic method to the preparation of a large number of pyrrole derivatives.

A third general synthetic method is that of Hantzsch. The method consists in the action of ammonia on a compound produced by the condensation of a ketonic ester with chloroacetone. In the original paper by Hantzsch,³ he synthesized α, α' -dimethyl- β -carboethoxyl pyrrole from acetoacetic ethyl ester, chloroacetone and ammonia. This type of reaction has been shown by Plancher⁴ to result in the first place in the formation of a chlorine compound, which with ammonia eliminates hydrogen chloride and water and produces a pyrrole derivative. He considered also that along with the intermediate product a furfurane derivative was formed. This method has been studied by Feist,⁵ and Korschun,⁶ but has found little application to general pyrrole synthesis.

¹ Gazz., 23, II, 300 (1893).

² Ibid., 44, I, 468 (1914).

³ Ber., 23, 1473 (1890).

⁴ Rend. Accad. Lincei, 13, I, 40 (1904).

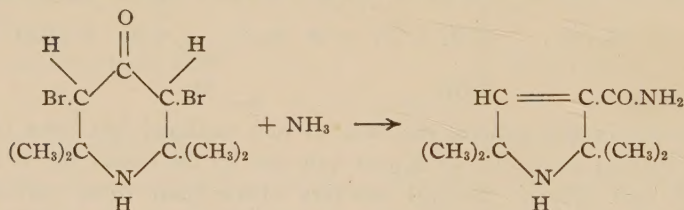
⁵ Ber., 35, 1545 (1902).

⁶ Ibid., 37, 2196 (1904).

A peculiar method of pyrrole synthesis from succinimide or maleinimide deserves mention. Succinimide, as is well known, is α, α' -diketo pyrrolidine, and maleinimide is α, α' -diketo pyrrole. Ciamician¹ and Anschutz² have shown that either of these imides reacts with phosphorus pentachloride producing first dichloromaleinimidochloride, then pentachloropyrrole, and finally heptachloropyrrole, the latter compound being easily reduced to tetrachloropyrrole. By means of potassium iodide this tetrachloropyrrole is easily changed to tetraiodopyrrole, which can be reduced by means of zinc and acetic acid to pyrrole itself.

Pyrrole derivatives are generally not easily reduced to pyrrolines or pyrrolidines, and consequently the methods for producing these hydrogenated pyrroles does not depend upon a reduction reaction. Only one general reaction has been devised for the production of pyrroline derivatives, but pyrrolidines have been prepared by a number of different synthetic methods.

In the synthesis of a Δ_3 -pyrroline from dibromotriacetoneamine an ammonia, Pauly³ has shown a very interesting rearrangement, whereby a pyridine derivative is changed to a pyrroline.



This amide upon saponification changes to an acid, which when heated loses carbon dioxide and gives rise to α, α' -tetramethyl- Δ_3 -pyrroline.

Heilscher⁴ has synthesized a Δ_2 -pyrroline by the action of ammonia on methyl- γ -bromo propyl ketone, the compound thus produced being Δ_2 - α -methyl pyrroline. Markwalder⁵ by the action of aniline and *p*-toluidine on the same bromoketone has synthesized N-phenyl- Δ_2 - α -methyl pyrroline and N-*p*-toluidino- Δ_2 - α -methyl pyrroline. This kind of a reaction is certainly capable of considerable extension toward the synthesis of pyrrolines, but thus far only the compounds listed above have been produced by this method.

Ladenburg,⁶ in 1886, following his preparation of piperidine from pentamethylene diamine, synthesized pyrrolidine by heating tetramethylene diamine. The two ends of this diamine were joined together by the elim-

¹ Gazz., 13, I, 403 (1883).

² Ann., 263, 156 (1891); 295, 27 (1897).

³ Ber., 32, 2000 (1899); Ann., 322, 77 (1902).

⁴ Ber., 31, 277 (1898).

⁵ J. prakt. Chem., 11, 75, 327 (1907).

⁶ Ber., 19, 782 (1886); 20, 442 (1887).

ination of ammonia. By the use of this simple reaction, Oldach¹ prepared β -methyl pyrrolidine from 2-methyl-tetramethylene diamine, and Tafel² prepared α, α' -dimethyl pyrrolidine from the phenyl hydrazone of acetonyl acetone. Knowalow³ likewise has used this synthetic method in preparing α, α' -tetramethyl pyrrolidine from symtetramethyl-tetramethylene diamine.

In 1899, Gabriel⁴ synthesized pyrrolidine by the elimination of hydrogen chloride from a molecule of 4-chlorobutylamine. In this category we may include the synthesis by Merling⁵ of α, α' -dimethyl pyrrolidine by heating hydrochlorbutallylmethylcarbinamine $[\text{CH}_3\text{CH}(\text{Cl})\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_3]$. To this same type of reaction also belongs the reaction by which J. V. Braun⁶ produced N-propyl, and N-ethyl pyrrolidine, by the action of propyl and ethyl amine respectively on 1,4-diiodobutane; but he must not be regarded as introducing this method for Scholtz and Friemehl⁷ had already used 1,4-dibromobutanes with amines to prepare pyrrolidine derivatives.

Willstätter⁸ has applied the Gabriel type of synthesis to the production of pyrrolidincarboxylic acids. He has synthesized α -pyrrolidincarboxylic acid and N-methyl- α -pyrrolidincarboxylic acid, by the action of ammonia and methyl amine, respectively, on 2,5-dibromopropylmalonic ester. The reaction, in the first place, resulted in the formation of a diamide or a dimethyl amide of the pyrrolidindicarboxylic acid, which upon saponification and elimination of carbon dioxide produced a mono-pyrrolidincarboxylic acid. Willstätter and Lessing⁹ have synthesized N-methyl- α, α' -pyrrolidindicarboxylic acid by the action of methyl amine on 2,5-dibromoadipinic ester.

Löffler¹⁰ in 1909, devised a pyrrolidine synthesis, which he has shown to admit of wide extension. By treating N-methyl-*n*-butyl amine with hypobromous acid, he obtained N-methylbromo-*n*-butylamine, which upon addition of concentrated sulfuric acid, lost hydrogen bromide and gave rise to N-methylpyrrolidine. He has applied this method further,¹¹ in preparing the N-methyl- β -methyl, N-methyl- α -methyl, N-methyl- α -ethyl and N-methyl- α -propyl derivatives of pyrrolidine.

It is interesting to note that until 1915, no instance in the literature

¹ *Ber.*, 22, 1858 (1889).

² *Ibid.*, 20, 1654 (1887).

³ *C.*, 1905, 2, 830.

⁴ *Ber.*, 32, 848 (1899).

⁵ *Ann.*, 264, 310 (1891).

⁶ *Ber.*, 44, 1252 (1911).

⁷ *Ibid.*, 24, 3231 (1891).

⁸ *Ibid.*, 32, 1290 (1899).

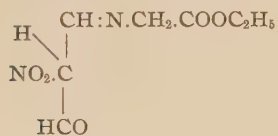
⁹ *Ibid.*, 35, 2065 (1902).

¹⁰ *Ber.*, 42, 3427 (1909).

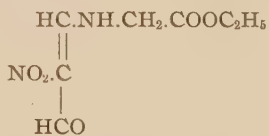
¹¹ *Ibid.*, 43, 2035 (1910).

may be found whereby pyrrole, pyrrolidine or their derivatives have been produced by the condensation of aldehydes and amines. The closest approach to such a reaction is given by Harries,¹ who synthesized pyrrole by the action of ammonia on succinic dialdehyde. He found that a dioxime was first formed and this on the elimination of water and ammonia changed to pyrrole.

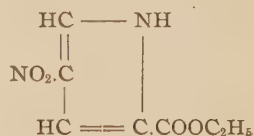
Hale and Hoyt² in 1915 published a paper on the constitution of the isomeric nitrocarbopyrrolic acids. The proof of the constitution of these acids depended upon the constitution of β' -nitro- α -carbopyrrolic acid, which was prepared by a condensation reaction. It had been shown previously that nitromalonic aldehyde, first prepared by Hill and Sanger³ in 1882 was a very reactive compound in entering into condensation reactions. Hill and Torrey⁴ had found that its sodium salt reacts readily with amines, such as aniline, *p*-toluidine, hydrazine, and phenylhydrazine, and by Hill⁵ and others⁶ it had been shown to condense even with such compounds as acetone, methyl-ethyl ketone and acetoacetic ester, in which condensations only methylenic hydrogen atoms were involved. All of these condensation reactions resulted in the formation of cyclic compounds, with the exception of aniline and *p*-toluidine, which formed only mono- or di-condensation products. From the marked activity of this di-aldehyde, Hale and Hoyt were led to expect pyrrole formation as a result of a condensation between glycine ethyl ester and nitromalonic aldehyde. Their expectations were realized in the production of β' -nitro- α -carbopyrrolic ethyl ester from these two compounds. By carrying out the condensation of these two substances in water solution they obtained a compound to which they assigned formula (I). Hale and Honan⁷ have shown, however, that this nitro aldehyde must have the formula as given in (II) owing to the fact that it is a secondary amine and will not form any salt with metals. By means of sodium hydroxide as a condensing agent, Hale and Hoyt were able to involve further the aldehydic oxygen in condensation with the α -methylenic hydrogen atoms to form β' -nitro- α -carbopyrrolic ethyl ester (III).



(I).



(II).



(III).

¹ Ber., **34**, 1488 (1901); **37**, 2538 (1904).

² J. Am. Chem. Soc., **37**, 2538 (1915).

³ Ber., **15**, 1906 (1882).

⁴ Am. Chem. J., **22**, 89 (1899).

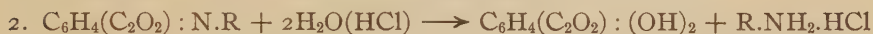
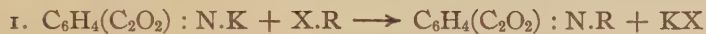
⁵ Ibid., **22**, 89 (1899).

⁶ Ibid., **24**, 1 (1900).

⁷ J. Am. Chem. Soc., **41**, 770 (1919).

The pyrrole derivative mentioned above was obtained directly without the isolation of the intermediate nitro-aldehyde by using alcoholic sodium hydroxide as a condensing medium. Hale and Hoyt proved conclusively the structure of this pyrrolic acid, and at the same time introduced a new mode of pyrrole formation, limited primarily to the production of nitro-pyrroles. The work of Hale and Honan¹ has shown that pyrrole formation may result by the action of nitromalonic aldehyde and β -alanine ethyl ester although the reaction product is very difficult of isolation. The present investigation is primarily a continuation of the study of this method of pyrrole formation.

In 1887, Gabriel² after investigating the use of potassium phthalimide as practiced by Graebe and Pictet³ announced a new method for the preparation of primary amines. He had been forced to try this method because of the very unsatisfactory yield of benzylamine realized from the action of ammonia on benzyl chloride. The reactions which are involved are as follows:



By this method the hydrochloride salt of the amine is obtained which can be converted into the free amine if so desired. The method was at once favorably received, inasmuch as it precluded any possibility of secondary or tertiary amine formation, a possibility which is always present and too often realized in the most general method for the preparation of primary amines, namely, the action of ammonia on organic halides. In the course of a few years, during which the method was tried by a number of investigators, it was found to offer a means of preparing any desired amine, if it were possible to prepare the corresponding halogen compound, provided of course that the halogen is not so firmly bound to the carbon-rest, as to fail to react with the potassium atom in potassium phthalimide. Inasmuch as amino ketones and amino acids are very widely used in chemical work, and also because their preparation by the old method is both laborious and unsatisfactory, their preparation by the Gabriel method was started at once. Aminoacetone,⁴ aminoacetophenone,⁵ aminopropiophenone⁶ and numerous others appeared in a short time.

In 1889, Chr. Schmidt¹ announced the preparation of an aminopropiophenone. He obtained this amine as its hydrochloride by the hydrolysis of a phthalyl propiophenone obtained by the action of potassium phthal-

¹ *Loc. cit.*

² *Ber.*, **20**, 2224 (1887).

³ *Ibid.*, **17**, 1173 (1884).

⁴ *Ber.*, **21**, 2684 (1888).

⁵ *Ibid.*

⁶ *Ibid.*, **22**, 3252 (1889).

imide on a brompropiphenone, the result of brominating propiphenone in carbon disulfide solution. Schmidt regarded this amine as α -aminopropiphenone, but he had no conclusive proof for his conclusion. It remained for Gabriel¹ in 1908 to show conclusively that Schmidt had obtained α -aminopropiphenone and not the beta derivative. Gabriel prepared these two derivatives, the alpha and beta, by methods which proved their constitution and showed the identity of his alpha amine with that of Schmidt's. He, however, gave only a chlorine analysis, a chloroplatinate salt and its analysis, and a picrate salt as analytical data on β -aminopropiphenone hydrochloride.

Thus, from an examination of the literature relative to this investigation, we find that β -aminopropiphenone had been prepared in 1908 by Gabriel, and also that in addition to the methods devised by Knorr, Hantzsch, Ladenburg, Löffler and others, for pyrrole synthesis, a new method which might involve the use of this amino ketone had been used successfully by Hale and Hoyt.

II.

Theoretical Part.

The preparation of β -aminopropiphenone is described but once in the literature. Further than this no reference to it may be found. It became our duty, therefore, to study as many methods for its preparation as possible, and to select that method which we believe to be the most advantageous for its preparation. Following the suggestions of a number of investigators in the preparation of amino ketones we have gone through the methods which will be outlined shortly. Of the several methods for the preparation of amines only a few can find application where a keto group is present. Of these, the preparation, whereby ammonia is used, is to be disregarded because our work has shown that the formation of secondary and tertiary amines is too likely of occurrence. The Gabriel synthesis is, therefore, the only one to be trusted to produce only the desired amine.

The first method for our discussion, naturally, is that method which is described in the literature, namely, the Gabriel method. This synthesis was carried out by Gabriel in the following series of reactions:

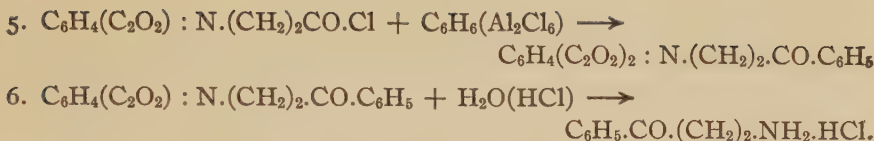
1. ${}^2\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N.K} + \text{Br}(\text{CH}_2)_3\text{Br} \longrightarrow \text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_3\text{Br}$
2. ${}^3\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_3\text{Br} + \text{KOH} \longrightarrow \text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_3\text{OH}$
3. $\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_3\text{OH} + 2\text{O} \longrightarrow \text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_2\text{COOH}$
4. ${}^4\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_2\text{COOH} + \text{PCl}_5 \longrightarrow$
 $\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N}(\text{CH}_2)_2\text{CO.Cl}$

¹ *Ber.*, 41, 242 (1908).

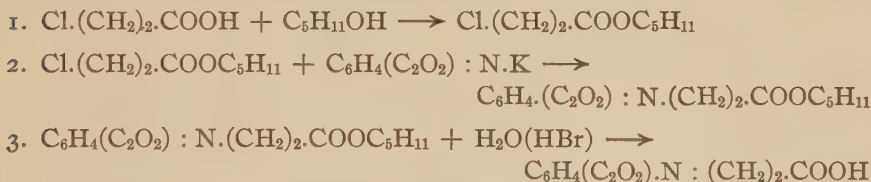
² *Ibid.*, 21, 2669 (1888).

³ *Ibid.*, 38, 633 (1905).

⁴ *Ibid.*, 41, 247 (1908).



The Gabriel synthesis does not result in a very good yield of final product. The main objection lies in the fact that the first reaction has a tendency to form the di-phthalyl derivative, which naturally materially lessens the yield of the mono-phthalyl compound. The hydrolysis reaction also is open to the objection that phthalamic acids are likely of formation; and the oxidation reaction (3) is one which is always capable of poor yields. Added to all these difficulties we were faced with the shortage of the necessary chemical trimethylene bromide and we, therefore, chose a divergence from the Gabriel method is so far as the preparation of β -phthalyl propionic acid is concerned. The following series of reactions show the method which we devised for the preparation of this acid:



The reaction of β -chloropropionic isoamyl ester with potassium phthalimide to produce β -phthalyl propionic isoamyl ester is a point in keeping with the findings of Weizzmann.¹ We found further that β -iodopropionic isoamyl ester reacted just as readily with potassium phthalimide as the corresponding chloro-ester. This reaction of the isoamyl ester of these two acids with potassium phthalimide is a rather surprising fact when we take into consideration that Holm² has reported that β -iodopropionic ethyl ester will not react with potassium phthalimide to produce the corresponding phthalyl derivative. We found in confirmation of this fact that even β -chloropropionic ethyl ester in its reaction with potassium phthalimide offers the same difficulties as reported by Holm. All the reactions outlined above proceeded very readily and in good yield with the exception of reaction (3), namely, the hydrolysis of the isoamylester of β -phthalyl propionic acid to the free acid. Sodium hydroxide could not be used here because of the formation of phthalamic acid derivatives by the hydrolysis of the phthalyl end of the chain, and hence we resorted to the use of hydrobromic acid as suggested by Weizzmann.³ The reaction, however, never yielded more than 40% of the theoretical quantity of β -phthalyl propionic

¹ *Proc. Chem. Soc.*, 28, 103 (1912).

² *Arch. Pharm.*, 242, 602 (1904).

³ *Loc. cit.*

acid and as a result we were unable to improve the Gabriel method of producing this acid in so far as the yield was concerned.

In the two methods just given for the preparation of the desired amino ketone it will be noted that potassium phthalimide enters into the synthesis at either the first or second step. This reaction is always attended by more or less difficulty and poor yields are often obtained. We hoped, therefore, that by carrying out this reaction towards the end of the synthesis we could obtain better yields of the final product. Inasmuch as we can only introduce the phenyl group by means of the Friedel-Crafts' reaction we sought to introduce this group and the keto group before the reaction with potassium phthalimide. The following series of reactions illustrate our method completely:

1. $\text{Cl} \cdot (\text{CH}_2)_2 \cdot \text{COOH} + \text{PCl}_3 \longrightarrow \text{Cl} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{Cl}$
2. $\text{Cl} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{Cl} + \text{C}_6\text{H}_6(\text{Al}_2\text{Cl}_6) \longrightarrow \text{Cl} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$
3. $\text{Cl} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5 + \text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N} \cdot \text{K} \longrightarrow$
 $\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$
4. $\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) : \text{N} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5 + \text{H}_2\text{O}(\text{HCl}) \longrightarrow$
 $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot (\text{CH}_2)_2 \cdot \text{NH}_2 \cdot \text{HCl}$

We found that all of the reactions proceeded readily to produce an excellent yield of final product. The β -chloropropiophenone was prepared according to the method of Collet,¹ which we varied to suit the reaction in hand.

This last synthesis for β -aminopropiophenone was finally modified to use β -iodopropionic acid as a starting product, inasmuch as it is easier of preparation than β -chloropropionic acid. We attempted both the DeBarr² and Jacobs-Heidelberger³ methods for the preparation of the chloro acid, but found that good results could not be obtained by either process, although the latter gave by far the better product. Inasmuch as β -iodopropionic acid is easily prepared by the Victor Meyer⁴ method and reacts as well as the chloro derivative we recommend its use in this synthesis. Reaction (1) and (2) outlined above, give 90% of the theoretical amount of β -iodopropiophenone; reaction (3) gives 70% of the theoretical amount of β -phthalyl propiophenone; and the last reaction is practically quantitative.

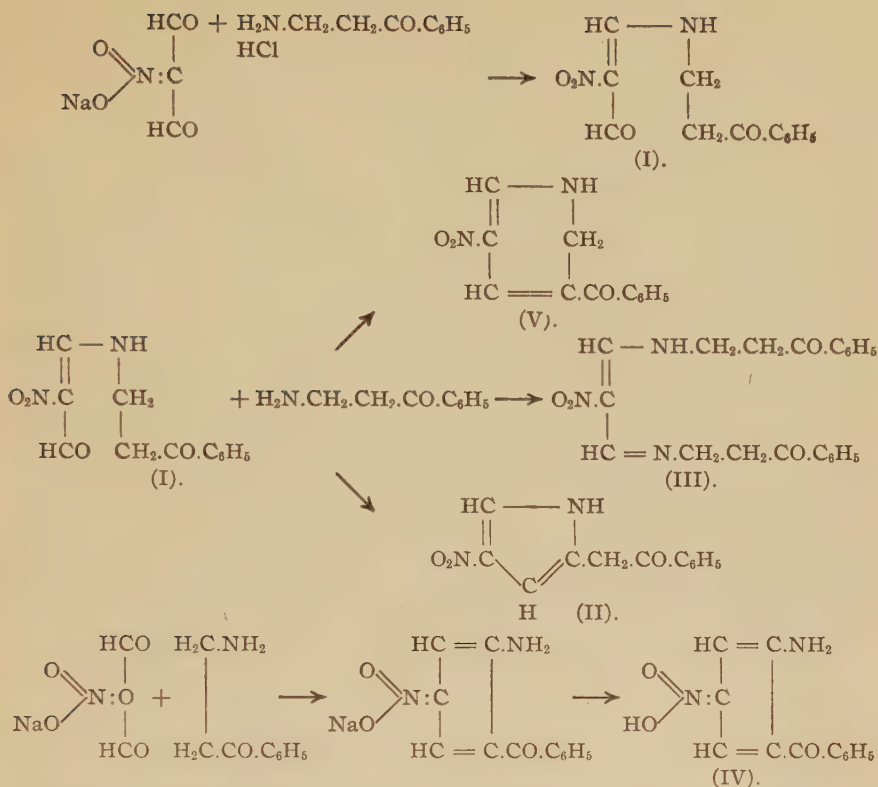
The work of several investigators on the subject of the condensation of amines with nitromalonic aldehyde led us to the expectation of at least four different products from the action of sodium nitromalonic aldehyde and β -aminopropiophenone hydrochloride. We list below all the possible condensations which may occur between these two compounds.

¹ *Bull. soc. chim.*, [3] 17, 80 (1897).

² *Am. Chem. J.*, 22, 334 (1899).

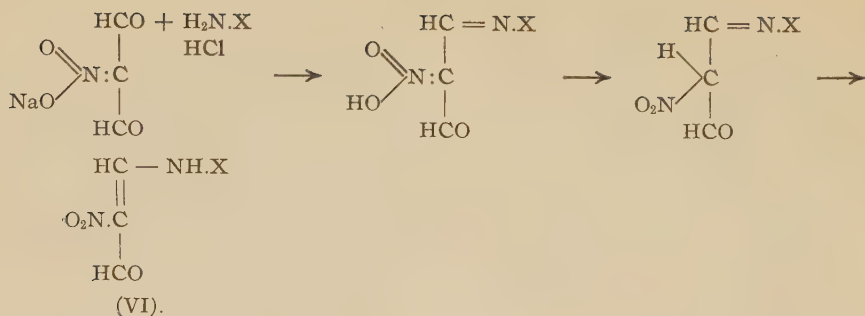
³ *J. Am. Chem. Soc.*, 39, 1465 (1917).

⁴ *Ber.*, 21, 24 (1888).



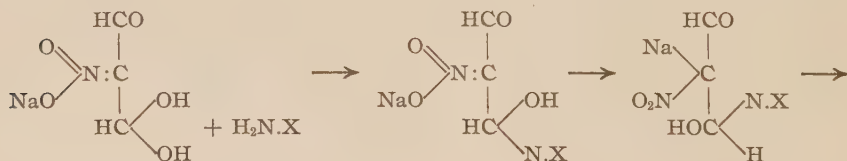
Previous work by Hill and Torrey and by Hale and Hoyt on the condensation of the 1,3-dialdehyde and compounds in which an amino group is adjacent to a methylenic group has shown that the primary condensation proceeds between the aldehyde group and the amino group. The primary condensation between sodium nitromalonic aldehyde and β -aminopropiophenone hydrochloride proceeds, therefore, to the formation of the acrolein derivative I, a 2-benzoyl- β -ethylamino- α -nitroacrolein, the reaction taking place by merely warming a water solution of equimolecular quantities of the two substances for two or three hours on the steam bath. Its constitution as an aldehyde was established through the usual silver mirror test for aldehydes, and a Liebermann nitrosoamine test gave positive evidence of the presence of the secondary amine group. The production here of a true nitro paraffin is in accordance with the work of Hale and Honan,¹ who have shown that the compounds resulting from the condensation of nitromalonic aldehyde and aniline, *p*-toluidine, glycine ethyl ester, and β -alanine ethyl ester, are true nitro paraffins, the reaction apparently proceeding as follows:

¹ *Loc. cit.*

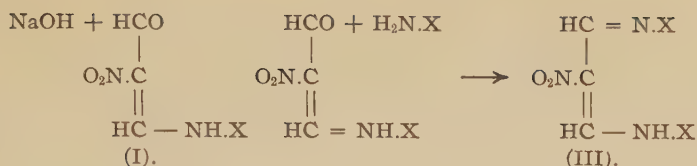


Here X represents the organic residue of the compounds listed above. These investigators were led to believe in the above interpretation of the reaction because of the fact that no metallic salts of the compounds (VI) could be produced. It, therefore, was very evident that either the true nitro form of the NO₂ group predominates entirely over its acidic isonitro form or that the hydrogen atom on the carbon atom containing this nitro group had shifted to the nitrogen atom to form a secondary amine thereby leaving no chance for the nitro group to assume its tautomerisic isonitro form. On the application of a secondary amine test on the compounds (VI), positive evidence of the presence of this group was shown and they were, therefore, led to the interpretation as given above in the equations of reaction.

Having established the constitution of 2-benzoyl-β-ethylamino-α-nitroacrolein, it is easy to understand the formation of compound III. By carrying out the condensation of one mole of sodium nitromalonate aldehyde and two moles of β-aminopropiophenone hydrochloride in aqueous solution and in the presence of a little sodium hydroxide, we realize a copious white precipitate of this compound, a 2-benzoyl-α-ethylamino-2-benzoyl-γ-ethylimino-β-nitropropylene. During the course of the reaction the solution becomes more alkaline, and the amount of increase in alkalinity corresponds to that required from one mole of sodium hydroxide. This same type of reaction has already been reported by Hill and Torrey¹ as taking place between aniline and sodium nitromalonate aldehyde. We repeated this reaction and found that the amount of alkalinity produced corresponds to that of one mole of sodium hydroxide. The mechanism of this change may be assumed to take place in the following manner:



¹ *Loc. cit.*



It may be presumed from a consideration of this reaction that the primary condensation product I (already described) is produced in an analogous manner, except that the sodium atom of the aldehyde is immediately replaced by a hydrogen atom from the hydrochloric acid of the amine hydrochloride and then water is eliminated in the molecule instead of sodium hydroxide. In the case, however, of alkali being present the alkali added neutralizes the hydrochloric acid of the amine hydrochloride, thus permitting the formation of the sodium hydroxide.

The nitropropylene derivative gives a test for a secondary amine group, negative test for an aldehyde, and a platinum determination on its platinic chloride salt serves to check its molecular weight. This nitropropylene compound may be produced by the action of alkali or piperidine on an alcoholic solution of the nitroacrolein compound (I). We must assume at once that a hydrolysis of the nitroacrolein takes place producing free β -aminopropiophenone and sodium nitromalonic aldehyde, the free β -aminopropiophenone then condensing with unchanged nitroacrolein, to produce the nitropropylene derivative.

When the condensation of sodium nitromalonic aldehyde (one mole) and β -aminopropiophenone hydrochloride (one mole) is carried out in the presence of strong alcoholic sodium hydroxide and at a temperature of 50° , a red colored precipitate comes out from the deep red solution. From its formation under similar conditions from the nitroacrolein we can say at once that it is the pyrrole derivative α -phenacyl- β' -nitropyrrole (II). Its formation in either case may be regarded as the result of the condensation of the free aldehyde group in the nitroacrolein (I) with the two hydrogen atoms on the methylenic group adjacent to the amino group. The conditions herein described practically eliminate the formation of the nitropropylene which is formed under similar conditions except the temperature condition. This α -phenacyl- β' -nitropyrrole imparts the familiar red color to a pine-shaving moistened with hydrochloric acid and forms a chloroplatinic double salt as a result of the presence of the secondary amine group. We had hoped that by oxidation of this pyrrole to reduce the phenacyl group to a carboxyl group and thus arrive at the β' -nitro- α -carbopyrrolic acid of Hale and Hoyt,¹ but all our attempts in this direction were without success.

From the strongly alkaline mother liquor after the separation of the pyrrole, no more pyrrole can be isolated, either by evaporation to small

¹ *Loc. cit.*

volume or by long standing. Upon acidification, however, a brown amorphous precipitate appears, which proves to be the nitrocyclopentadiene derivative IV. In this compound the nitro group is always present as its acidic isonitro form, and hence the compound produces salts. The presence of the primary amino group was shown by the usual Hofmann carbylamine test, and all its other reaction and properties such as solubility and stability correspond closely to the nitrocyclopentadienes of Hale and Thorpe.¹ The compound forms no hydrochloride even though an amino group is present, and this is due to the presence of the strongly acidic isonitro group which renders very feebly basic the amino group. The only explanation that can be advanced for the formation of this cyclopentadiene arises from a consideration of the reaction whereby the nitroacrolein compound (I) is hydrolyzed in the presence of alkali to free β -aminopropiophenone and sodium nitromalonic aldehyde, and these two compounds then condense under the conditions imposed on the system to the 2-benzoyl-3-amino-5-nitrocyclopentadiene (IV).

It is, of course, possible on a theoretical basis to obtain a dihydropyridine derivative of the structure (V) from the condensation of the free aldehyde group of the nitroacrolein (I) with the two hydrogen atoms on the methylenic group adjacent to the keto group. However, we were not able to isolate such a compound, even though many varying conditions of condensation were presented. It must be inferred, therefore, that the two hydrogen atoms on the methylenic group adjacent to the amino group in this nitroacrolein derivative are more labile than those of the methylenic group adjacent to the keto group, although the keto group is supposed to render such hydrogen atoms very labile. Hale and Honan² have reported that neither a pyrrole derivative nor a pyridine derivative is produced by the condensation of β -alanine ethyl ester and sodium nitromalonic aldehyde, thereby showing that the carbethoxyl group has little if any activating effect on the methylenic groups near it. Inasmuch as we were able to obtain a pyrrole from our reaction outlined above we can at once assume that the keto group has a greater activating effect on neighboring methylenic hydrogen atoms than does the carbethoxyl group. We can state further that the phenyl group has little or no effect on the methylenic hydrogen atoms, since benzyl amine, a compound wherein a phenyl group is adjacent to the methylenic group, will not condense with nitromalonic aldehyde to produce a pyrrole derivative. In connection with this fact, we have shown that ethyl amine will not form a pyrrole derivative when condensed with this 1,3-dialdehyde, from which we can infer that a keto group must be present in the amino compound. In order to bring about pyrrole formation.

¹ *J. Am. Chem. Soc.*, **35**, 262 (1913).

² *Loc. cit.*

III.

Experimental Part.

Preparation of Potassium Phthalimide.—We mention here our procedure which has served to facilitate the general mode of operation. The phthalimide was prepared according to the method of Dunlap¹ from phthalic anhydride and urea. Twenty g. of phthalimide was dissolved in 400 cc. of hot absolute alcohol and to this hot solution 7.6 g. of potassium hydroxide, dissolved in 30 cc. of 75% alcohol, were added. The final solution was cooled at once and the potassium phthalimide which separates was filtered off. In this filtrate another portion of 20 g. of phthalimide was dissolved by warming, and immediately upon effecting this solution, 7.6 g. of potassium hydroxide in 30 cc. of 75% alcohol were added as above. The potassium salt finally separating was filtered off and together with the portion previously obtained well washed with acetone to remove any unacted upon phthalimide. The weight of the potassium phthalimide thus obtained from 40 g. of phthalimide amounted to 45 g.

β -Chloropropionic-isoamyl Ester, $\text{Cl}(\text{CH}_2)_2\text{COOC}_5\text{H}_{11}$.—Ten g. of β -chloropropionic acid, prepared according to the method of Jacobs and Heidelberger,² were dissolved in 8.2 g. of isoamyl alcohol and into the boiling solution, under reflux, a current of dry hydrogen chloride was led for one hour. The reaction mixture was then shaken with water and the alcoholic layer removed and dried over calcium chloride. The yield amounted to 90% of the theoretical. β -Chloropropionic isoamyl ester is a colorless liquid with pleasant odor and with the exception of ligroin and water is miscible with most organic solvents. The boiling point of the pure product is $207-8^\circ$ under 740 mm. pressure.

Calc. for $\text{C}_8\text{H}_{16}\text{O}_2\text{Cl}$: Cl, 19.85. Found: 19.54.

β -Iodopropionic-isoamyl Ester, $\text{I}(\text{CH}_2)_2\text{COOC}_5\text{H}_{11}$.—A portion of 20 g. of β -iodopropionic acid, prepared from glyceric acid and freshly prepared phosphorus iodide according to the method of Victor Meyer³ was converted into its isoamyl ester by exactly the same procedure as outlined above for the chloro derivative. The properties of this iodo ester are closely similar to those of the chloro ester. The pure product boils at 183° under 140 mm. with slight decomposition.

Calc. for $\text{C}_8\text{H}_{16}\text{O}_2\text{I}$: I, 46.99. Found: 46.50.

β -Phthalylpropionic-isoamyl Ester, $\text{C}_8\text{H}_{14}\text{O}_2$: $(\text{CH}_2)_2\text{COOC}_5\text{H}_{11}$.—18 g. of β -chloropropionic-isoamyl ester, or an equivalent amount of the corresponding β -iodopropionic-isoamyl ester, and 19 g. of potassium phthalimide were heated together in a sealed tube at 130° for one hour. The final product was repeatedly extracted with dry ether and the β -phthalyl-

¹ *Am. Chem. J.*, **18**, 333 (1896).

² *J. Am. Chem. Soc.*, **39**, 1465 (1917).

³ *Ber.*, **21**, 24 (1888).

propionic-isoamyl ester obtained at once upon the evaporation of the ethereal solution. The yield was 70% of the theoretical. This product is readily soluble in acetone, benzene, ethyl acetate, acetic acid or ether; fairly soluble in alcohol or chloroform; and insoluble in ligroin or water. The product as purified by crystallization from alcohol melts at 61°.

Calc. for $C_{16}H_{19}O_2N$: C, 66.41; H, 6.62; N, 4.84. Found: C, 66.89; H, 6.80; N, 4.86.

β -Phthalylpropionic Acid, $C_8H_4O_2:N.(CH_2)_2.COOH$.—Ten g. of β -phthalylpropionic-isoamyl ester and 125 cc. of hydrobromic acid (49%) were shaken together in a closed flask under gentle warming at 40°. After two hours, the reaction mixture was filtered and the aqueous filtrate diluted with water and sufficient sodium carbonate added to neutralize 90% of the hydrobromic acid present. Upon cooling the solution, colorless crystals of β -phthalylpropionic acid appeared. The yield amounted to 40% of the theoretical. The product is readily soluble in acetone, chloroform, ethyl acetate, acetic acid or ether; fairly soluble in alcohol, benzene, or water; and insoluble in ligroin. Crystallized from water the compounds melt at 150–1° exactly, as reported by Gabriel.¹

Preparation of β -Chloropropiophenone.—Ten g. (3 mols) of β -chloropropionic acid and 9 g. (2 mols) of phosphorus trichloride were heated together for one hour on a steam bath. To the warm mixture 100 cc. of benzene were added and the benzene solution of the acid chloride was removed from the insoluble phosphorus oxide portion by filtration. In order to involve only that chlorine present as acid chloride in this β -chloropropionyl chloride,² the benzene filtrate of the latter compound was now poured upon 15 g. (1 mol) of anhydrous aluminium chloride and the mixture gently warmed on a water bath, under reflux, for an hour. The final reaction mixture was now poured upon ice and a little ether added to effect a distinct separation of the two layers. The ether-benzene layer was removed, washed with water and dried over calcium chloride. Upon spontaneous evaporation, the β -chloropropiophenone appears in colorless crystals which purified by crystallization from alcohol, melt at 57–8°. The yield is 90% of the theoretical value. This same general procedure was employed by Collet,³ save for the necessary precautions,—as stated above, in carrying out the Friedel-Crafts reaction, and also in the method of purification. For the latter step Collet resorted to distillation *in vacuo* and obtained thus so little of the pure compound that he was able only to report its isolation through the formation of an anilide. The difficulty here experienced by Collet was explained later by Kohler⁴ who demonstrated the ease with which this compound underwent

¹ *Loc. cit.*

² A. Collet, *Bull. soc. chim.*, [3] 17, 66 (1897); J. Boeseken, *Ibid.*, 19, 349 (1898).

³ *Bull. soc. chim.*, [3] 17, 80 (1897).

⁴ *Am. Chem. J.*, 42, 375 (1909).

decomposition into hydrogen chloride and phenylvinyl ketone even *in vacuo*. The preparation of the pure compound by Kohler was accomplished by the direct addition of hydrogen chloride to phenylvinyl ketone in dry ether solution. The properties reported by Kohler agree with ours in every respect and hence the constitution as assigned by Kohler may find its verification in this method originated by Collet and amplified above.

β -Iodopropiophenone, $\text{I} \cdot (\text{CH}_2)_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$.—This compound may be prepared from β -iodopropionic acid and phosphorus trichloride and the subsequent treatment of the benzene solution with anhydrous aluminium chloride exactly in the manner as described for the preparation of β -chloropropiophenone above. β -Iodopropiophenone when crystallized from alcohol appears in colorless prisms which melt at 61° . It is readily soluble in most of the organic solvents save ligroin in which it is fairly soluble. It is insoluble in water.

Calc. for $\text{C}_9\text{H}_9\text{OI}$: C, 41.55; H, 3.49; I, 48.81. Found: C, 41.69; H, 3.44; I, 48.69.

The acid chloride produced here as an intermediate product is mentioned but once in the literature¹ with no word of its properties. We isolated a small quantity of it but could not determine its boiling point owing to the great ease with which decomposition set in. The acid chloride is exceedingly irritating to the eyes.

The Preparation of β -Phthalylpropiophenone.—17 g. of β -chloropropiophenone (or an equivalent amount of β -iodopropiophenone) and 19 g. of potassium phthalimide were intimately mixed and heated in a sealed tube during constant shaking for one hour at a temperature of 130 – 40° . The reaction mixture was then repeatedly extracted with benzene to remove the product. The clear benzene solution was subjected to distillation with steam to remove all of the benzene and traces of unacted upon chloropropiophenone (here dissociating into hydrogen chloride and phenylvinyl ketone). When the distillate comes over free of odor, the product in the flask may be considered free from impurities. The water in the flask is then decanted from the solid residue and the latter crystallized from alcohol. The β -phthalylpropiophenone thus obtained is a colorless, highly crystalline compound melting at 130° . The yield is 68% of the theoretical. The product is identical in all respects with that obtained by Gabriel save for the yellow color he reports as present. β -Phthalylpropiophenone is readily soluble in acetone, chloroform or benzene; fairly soluble in alcohol, ethyl acetate, ether or acetic acid; and insoluble in ligroin or water. As Gabriel reported only a nitrogen determination we checked the nitrogen and determined further the carbon and hydrogen.

¹ Abderhalden and Gressel, *Z. physiol. Chem.*, **74**, 472–80.

Calc. for $C_{17}H_{13}O_3N$: C, 73.1; H, 4.69; N, 5.02. Found: C, 72.92; H, 4.67; N, 4.84.

The Preparation of β -Aminopropiophenone Hydrochloride.—A mixture of 3 g. of β -phthalylpropiophenone, 12 cc. of glacial acetic acid, and 10 cc. of conc. hydrochloric acid (previously saturated at 0° with dry hydrogen chloride) were placed in a sealed tube and the contents heated at $145-50^\circ$ for one hour. The reaction mixture, removed from the tube, was evaporated to a small volume (but not to dryness) upon a steam bath. The syrup was now taken up in 25 cc. of water and filtered from the insoluble phthalic acid. The filtrate was then allowed to evaporate slowly to dryness in a current of air and at a temperature not exceeding 60° . For final purification the β -aminopropiophenone hydrochloride was crystallized from absolute alcohol. The melting point is 128° exactly as reported by Gabriel¹ and the yield is 95% of the theoretical. As no analysis is to be found in the literature we determined these values.

Calc. for $C_9H_{11}ON.HCl$: C, 58.43; H, 6.47; N, 7.55. Found: C, 58.18; H, 6.56; N, 7.35.

2-Benzoyl- β -ethylamino- α -nitro-acrolein, $C_6H_5.CO.(CH_2)_2.NH.CH:C(NO_2).CHO$ (I).—When 5 g. of β -amino-propiophenone in the form of its hydrochloride and 4.2 g. of sodium nitromalonic aldehyde (an equimolecular proportion) were dissolved in 50 cc. of water and the solution allowed to stand at 50° for 10–12 hours the precipitation of this acrolein compound is almost complete. The reaction mixture was then cooled and the orange-colored product filtered off. The yield is about 75% of the theoretical. Upon crystallization from alcohol the product appears in small prisms practically colorless and melting at 153° . This benzoyl-ethylamino-nitro-acrolein is readily soluble in acetone or glacial acetic acid; fairly soluble in alcohol, benzene, chloroform, ethyl acetate, or water; slightly soluble in ether; and insoluble in ligroin.

Calc. for $C_{12}H_{12}O_4N_2$: C, 58.02; H, 4.84; N, 11.34. Found: C, 58.59; H, 5.02; N, 11.35.

This nitro-acrolein derivative gives with silver nitrate the characteristic test for an aldehyde and by means of the Liebermann test a secondary amine group was shown to be present.

2-Benzoyl- α -ethylamino-2-benzoyl- γ -ethylimino- β -nitropropylene, $C_6H_5.CO.(CH_2)_2.NH.CH:C(NO_2).CH:N.(CH_2)_2.CO.C_6H_5$ (III).—Five g. of β -amino-propiophenone (2 mol.) and 2.1 g. of sodium nitromalonic aldehyde (1 mol.) were dissolved in 100 cc. of water, and 2 cc. of 20% sodium hydroxide solution added. A white precipitate appeared immediately. This precipitate filtered off and crystallized from alcohol, gave fine, colorless needle clusters melting at 145° . The yield is 84% of the

¹ *Loc. cit.*

theoretical amount. This nitropropylene derivative is readily soluble in acetone, chloroform or glacial acetic acid; fairly soluble in alcohol, benzene or ethyl acetate; and insoluble in ether, ligroin or water.

Calc. for $C_{21}H_{21}O_4N_3$: C, 66.47; H, 5.58; N, 11.08. Found: C, 66.59; H, 5.60; N, 11.07.

When a slight excess of chloroplatinic acid is added to an alcoholic solution of this nitropropylene compound an orange-colored precipitate appears at once. This product was filtered off, well washed with dil. hydrochloric acid and dried over sulfuric acid. It melted at 208° . By analysis it served well to check the value required for the molecular weight of the nitropropylene.

Calc. for $(C_{21}H_{21}O_4N_3)_2 \cdot H_2PtCl_6$: Pt, 16.71. Found: Pt, 16.60.

By the application of either the Hinsberg or Liebermann tests indication of the presence of a secondary amine was well marked. Upon boiling a portion of this nitropropylene compound with conc. hydrochloric acid and allowing the yellow solution to cool a precipitate of the nitro-acrolein derivative appears and β -amino-propiophenone may be shown to be present in the solution. This decomposition corresponds exactly with the decomposition in acid solution of the so-called nitromalonic di-anil reported by Hill and Torrey.¹ Upon the addition of sodium hydroxide to an aqueous solution of the nitro-acrolein derivative (I) the immediate precipitation of this colorless nitropropylene compound was observed. In all respects the precipitate here and that produced in the prescribed manner above were identical. In the hydrolysis of the acrolein derivative, which must have ensued, we should expect to find nitromalonic aldehyde left free in the solution in that the liberated β -amino-propiophenone must necessarily have combined with a portion of the unhydrolyzed acrolein derivative. The point was proved by concentration of the mother liquor to small volume and addition of hydrochloric acid. After a short time beautiful crystals of *sym*-trinitrobenzene made their appearance, a condensation distinctly characteristic of nitromalonic aldehyde.²

α -Phenacyl- β' -nitropyrrole, $C_8H_6 \cdot CO \cdot CH_2 \cdot C_4H_3N \cdot NO_2$ (II).—Equivalent quantities of β -amino-propiophenone hydrochloride (5 g.) and sodium nitromalonic aldehyde (4.2 g.) were dissolved in 25–30 cc. of 50% alcohol, and 15 cc. of 20% sodium hydroxide solution added. The red solution is warmed for a few moments and then allowed to stand at 50° . The red precipitate which slowly forms, is filtered off and washed with dil. alcohol. The yield is only 30% of the theoretical amount. Crystallization from alcohol yielded small, lemon-yellow prisms melting at 170° . α -Phenacyl- β' -nitropyrrole is readily soluble in acetone or glacial

¹ *Am. Chem. J.*, **22**, 100 (1899); see also Hale and Honan, *Loc. cit.*

² *Loc. cit.*

acetic acid; fairly soluble in alcohol, chloroform, benzene or ethyl acetate; and insoluble in ether, ligroin or water.

This same pyrrole may be prepared by mixing a portion (one g.) of the benzoyl-ethylamino-nitro-acrolein (I) with 70% alcohol (10 cc.) and adding to this suspension a 20% sodium hydroxide solution (3 cc.). After gently warming for a half hour at 50°, the reaction is complete and the pyrrole derivative may be filtered off and treated as above. The yield in this procedure is however, scarcely better than when carrying out the reaction between the original components.

Calc. for $C_{12}H_{10}O_2N_2$: C, 62.59; H, 4.35; N, 12.17. Found: C, 63.36; H, 4.26; N, 12.70.

In order to check the molecular weight of the pyrrole molecule the chloroplatinic salt of the compound was prepared in the usual manner. The orange-colored precipitate was thoroughly washed with dil. hydrochloric acid, then with water and finally with acetone, after which it was dried *in vacuo* over sulfuric acid. The compound decomposes above 300° without melting.

Calc. for $(C_{12}H_{10}N_2O_2)_2 \cdot H_2PtCl_6$: Pt, 22.43. Found: Pt, 21.97.

It was hoped that by means of an oxidizing agent we could reduce the side chain to a carboxyl itself and thus be able to check the constitution of the pyrrole through identification with the well-known β' -nitro- α -carbopyrrolic acid, previously established by Hale and Hoyt.¹ But all attempts at oxidation have failed. Alkali fusion mixtures were of course, disastrous, owing to the presence of the nitro group. The identification of a secondary amine in the pyrrole was easily accomplished through the agency of either the Hinsberg reaction or the Liebermann nitroso-amine reaction. The familiar pyrrole red color upon a pine stick moistened with hydrochloric acid was most marked. There can be little or no doubt concerning the structure we have assigned. The previous investigations of Hale and Hoyt have thoroughly established the course of the reaction.

The red alkaline mother liquor left after separating the pyrrole yielded no further quantity of pyrrole either upon long standing or upon slow evaporation to small bulk (temperature of 50°). When, however, the liquor was acidified there appeared a considerable quantity of a red amorphous precipitate. This precipitate no longer gives the characteristic tests for a pyrrole and shows a much less degree of solubility in the ordinary solvents than does the pyrrole itself. Its purification was brought about by solution in acetone and precipitation therefrom by addition of ligroin. The precipitate was then dissolved in hot alcohol and upon cooling the light brown or yellow amorphous product separates out. The product

¹ *Loc. cit.*

thus purified decomposes between 127° and 132° and analyzes well for 2-amino-3-benzoyl-5-nitro-cyclopentadiene (IV). This cyclopentadiene is readily soluble in chloroform, acetone, ethyl acetate or glacial acetic acid; fairly soluble in alcohol; slightly soluble in benzene; and insoluble in ether, ligroin or water.

Calc. for $C_{12}H_{10}O_3N_2$: C, 62.59; H, 4.35; N, 12.17. Found: C, 62.00; H, 4.50; N, 12.50.

The hydrolysis of the acrolein derivative in the presence of alkali, as stated in an earlier part, undoubtedly makes possible the condensation between nitromalonic aldehyde and the two methylene groups of the liberated amino ketone. Of course too great a concentration of alkali is likely to decompose this amino ketone so soon as liberated but this does not occur with the concentration of alkali employed by us. The cyclopentadiene thus made possible of formation contains an isonitro group and readily forms salts. The free substance cannot be precipitated from its alkali salts by the addition of carbon dioxide and thus is analogous to the nitro-cyclopentadiene described by Hale.¹

Aniline and Sodium Nitromalonic Aldehyde.—Following the directions of Hill and Torrey¹ a slight excess of aniline (2 mol.) was added to one mole of sodium nitromalonic aldehyde in dilute alcoholic solution. The solution turns yellow and after standing three or four days a yellow crystalline product separates out. The precipitate was filtered off and the filtrate extracted two or three times with ether. The solution after ether extraction was then titrated with hydrochloric acid and one mole of sodium hydroxide, calculated on the basis of the aldehyde entering into reaction, was present. The precipitate of the di-anil gives a test for a secondary amine using the Hinsberg test. The Liebermann nitrosoamine test cannot be applied because the di-anil is decomposed by acids. A chloroplatinic salt was made of this di-anil in the usual manner and when washed with ether, dried and then analyzed gave a good check on the molecular weight.

Calculated for $(C_{15}H_{13}O_2N_2)_2H_2PtCl_6$: Pt, 20.67. Found: Pt, 20.15.

Ethyl Amine, Benzyl Amine and Sodium Nitromalonic Aldehyde.—No quantitative experiments were carried out in the reaction of ethyl amine and the aldehyde. When these two substances are dissolved in water or dilute alcoholic medium, condensation takes place involving two moles of the amine and one of the aldehyde. The reaction mixture becomes strongly alkaline during the course of the reaction, and an amount of sodium hydroxide approximately equivalent to one mole is produced. The product a yellow, low-melting solid, gave negative tests for a pyrrole and positive test for the secondary amine, using the Hinsberg test.

¹ *Loc. cit.*

The same procedure was applied to the action of benzyl amine and sodium nitromalonic aldehyde, and similar results were obtained. The product, however, is a higher melting point solid and is not as unstable in the presence of acids as the product realized from ethyl amine and sodium nitromalonic aldehyde.

Summary.

In this investigation we have shown that the best method of preparing β -aminopropiophenone is one involving the action of β -iodopropiophenone and potassium phthalimide, and the subsequent hydrolysis of β -phthalylpropiophenone produced by this reaction to the amine by means of hydrochloric acid. We have also studied the condensation of β -aminopropiophenone with sodium nitromalonic aldehyde and have found that four condensation products are formed, namely, 2-benzoyl- β -ethylamino- α -nitroacrolein, 2-benzoyl- α -ethylamino-2-benzoyl- γ -ethylimino- β -nitropropylene, α -phenacyl- β' -nitropyrrole, and 2-amino-3-benzoyl-5-nitrocyclopentadiene. The first compound is formed by the condensation of one mole of the aldehyde with one mole of the amine in neutral water solution; the second compound is produced by the condensation of one mole of the aldehyde and two moles of the amine in dilute aqueous sodium hydroxide solution; and the third and fourth compounds are produced together when condensation occurs between the aldehyde and amine in strong alcoholic sodium hydroxide medium. By an examination of the reactions between aniline, ethyl amine or benzyl amine and sodium nitromalonic aldehyde we have found that in each case, sodium hydroxide and a secondary amine is formed, a point in keeping with our explanation of the reaction whereby the nitropropylene compound is produced.

